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=> d his

(FILE 'HOME' ENTERED AT 14:20:25 ON 20 JUL 2004)

FILE 'MEDLINE' ENTERED AT 14:20:59 ON 20 JUL 2004

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L1         68418 S RETINO?
L2          2524 S RAR
L3           357 S L2 AND ANTAGONIST?
L4            13 S L3 AND KERATIN?
L5          3655 S L1 AND ANTAGONIST?
L6            12 S L5 AND KERATINIZATION
L7            19 S L2 AND PSORIASIS
L8             5 S L7 AND ANTAGONIST?
L9             5 S L7 AND AGONIST?
L10            1 S L9 NOT L8
L11          505 S L1 (L) PSORIASIS
L12           12 S L11 (P) AGONIST?
L13           23 S L11 AND ANTAGONIST?
L14            6 S L12 AND L13
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L1 68418 S RETINO?
L2 2524 S RAR
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=> s l1 and antagonist?
469098 ANTAGONIST?
L5 3655 L1 AND ANTAGONIST?

=> s l5 and keratinization
2197 KERATINIZATION
L6 12 L5 AND KERATINIZATION

=> d 1-12 bib abs

L6 ANSWER 1 OF 12 MEDLINE on STN
AN 2001539396 MEDLINE
DN PubMed ID: 11586072
TI **Retinoids**--which dermatological indications will benefit in the near future?.
AU Zouboulis C C
CS Department of Dermatology, University Medical Center Benjamin Franklin, The Free University of Berlin, Berlin, Germany.. zouboulis@medizin.fu-berlin.de
SO Skin pharmacology and applied skin physiology, (2001 Sep-Oct) 14 (5) 303-15. Ref: 90
Journal code: 9807277. ISSN: 1422-2868.
CY Switzerland
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200112
ED Entered STN: 20011008
Last Updated on STN: 20020122
Entered Medline: 20011204
AB **Retinoids** are compounds with pleiotropic functions and a relatively selective targeting of certain skin structures. They are vitamins, because **retinol** (vitamin A) is not synthesized in the body and must be derived from diet, but also hormones with intracrine activity, because **retinol** is transformed into molecules that bind to nuclear receptors, exhibit their activity, and are subsequently inactivated. **Retinoids** exert their effects on target cells by binding and activating nuclear **retinoid** receptors. **Retinoid** receptors bind their ligands in form of dimers. Heterodimers can be formed between two different **retinoid** receptor molecules but also between **retinoid** X receptors and the vitamin D receptor as well as the triiodothyronin receptor. This fact indicates complex interactions between **retinoids** and further hormonal signal transduction molecules. Interaction of **retinoid** receptors with transcriptional factors activated by other signal transduction mechanisms, e.g. AP-1, may provide dissociation of the **retinoid** effects. **Retinoids** can exhibit agonistic activity but also be neutral **antagonists** and inverse agonists. Topical and oral **retinol**, tretinoin, isotretinoin, and bexarotene, topical alitretinoin, retinaldehyde, motretinide, adapalene, tazarotene, and systemin acitretin compose the list of launched **retinoids.** Psoriasis and related disorders, congenital disorders of **keratinization**, acne, photoaging and hypovitaminosis A are classical approved indications of **retinoid** treatment, whereas cutaneous T-cell lymphoma, AIDS-associated Kaposi's sarcoma, acute promyelocytic leukemia and actinic lentigines were currently confirmed. In addition, **retinoids** have been successfully used in several other dermatoses, e.g. epithelial precanceroses and tumors, seborrhea, rosacea and acneiform dermatoses, lichen planus, eosinophilic folliculitis, condylomata accuminata, lichen sclerosus and atrophicus. Highly receptor selective molecules, **retinoic** acid receptor-beta-inducers, AP-1 complex **antagonists**, and inverse agonists will be probably lead the **retinoid** development in the near future. New, more effective and less toxic **retinoids**, alone or in combination with other drugs and new delivery systems may provide therapeutic solutions for benign and malignant proliferative skin

diseases, such as psoriasis and non-melanoma tumors, cancer chemoprevention and differentiation therapy.

L6 ANSWER 2 OF 12 MEDLINE on STN
AN 2000200553 MEDLINE
DN PubMed ID: 10734183
TI R115866 inhibits all-trans-**retinoic** acid metabolism and exerts **retinoidal** effects in rodents.
AU Stoppie P; Borgers M; Borghgraef P; Dillen L; Goossens J; Sanz G; Szel H; Van Hove C; Van Nyen G; Nobels G; Vanden Bossche H; Venet M; Willemsens G; Van Wauwe J
CS Janssen Research Foundation, Beerse, Belgium.
SO Journal of pharmacology and experimental therapeutics, (2000 Apr) 293 (1) 304-12.
Journal code: 0376362. ISSN: 0022-3565.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200004
ED Entered STN: 20000505
Last Updated on STN: 20000505
Entered Medline: 20000421
AB All-trans-**retinoic** acid (RA) regulates epithelial differentiation and growth through activation of specific nuclear RA receptors (RARs). Because high-rate metabolism largely impairs the biological efficacy of RA, we have sought for compounds capable of inhibiting the metabolic breakdown of the **retinoid**. This study identifies R115866 as a novel inhibitor of the cytochrome P450 (CYP)-mediated metabolism of RA. In vitro, nanomolar concentrations of R115866 inhibited the conversion of RA by CYP26, a RA-inducible RA metabolizing enzyme. In vivo, oral administration of R115866 (2.5 mg/kg) to rats induced marked and transient increases of endogenous RA levels in plasma, skin, fat, kidney, and testis. Consistent with its ability to enhance endogenous RA content in tissues, R115866 was found to exert **retinoidal** activities. Like RA, the title compound: 1) inhibited vaginal **keratinization** in estrogen-stimulated rats; 2) induced epidermal hyperplasia in mouse ear skin; 3) transformed mouse tail epidermis from a para- to an orthokeratotic skin type; and 4) up-regulated the CYP26 mRNA expression in rat liver. Furthermore, we found that the **keratinization**-suppressive and CYP26-inducing activities of R115866 could be reversed by concomitant administration of the RAR **antagonist**, AGN193109. Our data characterize R115866 as a potent, orally active inhibitor of RA metabolism, capable of enhancing RA levels and displaying **retinoidal** actions. These activities are reversed by RAR antagonism, supporting the idea that the actions of R115866 result from increased availability of endogenous RA and improved RAR triggering.

L6 ANSWER 3 OF 12 MEDLINE on STN
AN 1999251117 MEDLINE
DN PubMed ID: 10234809
TI Expression of **retinoic** acid receptor beta is associated with inhibition of **keratinization** in human head and neck squamous carcinoma cells.
AU Zou C P; Hong W K; Lotan R
CS Department of Thoracic/Head and Neck Medical Oncology, University of Texas M.D. Anderson Cancer Center, Houston 77030, USA.
NC PO1 CA 52051 (NCI)
R25 CA57730 (NCI)
SO Differentiation; research in biological diversity, (1999 Jan) 64 (2) 123-32.
Journal code: 0401650. ISSN: 0301-4681.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199905
ED Entered STN: 19990607
Last Updated on STN: 19990607
Entered Medline: 19990525
AB The preventive effects of **retinoids** on oral carcinogenesis may be related to their ability to modulate the growth and differentiation of human oral squamous epithelial cells. Nuclear **retinoid** receptors (RAR alpha, beta, and gamma, and RXR alpha, beta, and gamma) may mediate these effects by regulating gene transcription. The removal of serum from the growth medium of two head and neck squamous cell carcinoma

lines 1483 and SqCC/Y1 resulted in a decrease in RAR beta mRNA level and concurrent increases in the expression of the keratin K1 and transglutaminase type I (TGase I), which are markers of differentiation of keratinizing squamous epithelial cells. All-trans-**retinoic** acid (tRA) or 13-cis-RA increased RAR beta and decreased K1 and TGase I mRNA levels in serum-free medium. Transcriptional activation of reporter genes by means of **retinoid** response elements (RARE and RXRE) indicated that the RXR-RAR pathway predominates over the RXR homodimer pathway in the 1483 cells. Among several synthetic **retinoids** with preference for binding to specific nuclear **retinoid** receptors, those that induced RAR beta also suppressed K1. The inverse association between RAR beta expression and K1 and TGase I levels implicates this receptor in suppression of **keratinization** in oral epithelial cells.

L6 ANSWER 4 OF 12 MEDLINE on STN
AN 92229321 MEDLINE
DN PubMed ID: 1565989
TI [**Retinoids** in dermatology].
Retinoides en dermatologie.
AU Saurat J H
CS Clinique et Policlinique de Dermatologie, hopital cantonal universitaire, Geneve.
SO La Revue du praticien, (1992 Jan 1) 42 (1) 69-75. Ref: 18
Journal code: 0404334. ISSN: 0035-2640.
CY France
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA French
FS Foreign
EM 199205
ED Entered STN: 19920607
Last Updated on STN: 19920607
Entered Medline: 19920519
AB **Retinoids** are natural substances, similar to vitamin A, and acting through nuclear receptor on the gene transcription, with a similar mechanism to steroid hormones. Synthetic **retinoids** are used in the treatment of different skin diseases including severe acne, abnormal **keratinization**, psoriasis, epidermoid carcinoma, and inflammatory skin lesions. Systemic or local administration of these compounds acts on the proliferation and differentiation of the skin structure by not clearly understood pathway. This pathway could be either an agonist, **antagonist** or substitutive modulation of the natural **retinoid** action or a separate pathway. The different drugs have in common, teratogenic properties, which limit their usefulness.

L6 ANSWER 5 OF 12 MEDLINE on STN
AN 91208220 MEDLINE
DN PubMed ID: 1708287
TI TGF-beta and **retinoic** acid: regulators of growth and modifiers of differentiation in human epidermal cells.
AU Choi Y; Fuchs E
CS Howard Hughes Medical Institute, Department of Molecular Genetics and Cell Biology, University of Chicago, Illinois 60637.
NC AR31737 (NIAMS)
SO Cell regulation, (1990 Oct) 1 (11) 791-809.
Journal code: 9005331. ISSN: 1044-2030.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199105
ED Entered STN: 19910616
Last Updated on STN: 19960129
Entered Medline: 19910528
AB In the epidermis of skin, a fine balance exists between proliferating progenitor cells and terminally differentiating cells. We examined the effects of TGF-beta s and **retinoic** acid (RA) on controlling this balance in normal and malignant human epidermal keratinocytes cultured under conditions where most morphological and biochemical features of epidermis in vivo are retained. Our results revealed marked and pleiotropic effects of both TGF-beta and RA on keratinocytes. In contrast to **retinoids**, TGF-beta s acted on mitotically active basal cells to retard cell proliferation. Although withdrawal from the cell cycle is a necessary prerequisite for commitment to terminal differentiation, TGF-beta s inhibited normal **keratinization** in suprabasal cells and promoted the type of differentiation commonly associated with

wound-healing and epidermal hyperproliferation. The actions of TGF-beta s and RA on normal **keratinization** were synergistic, whereas those on abnormal differentiation associated with hyperproliferation were **antagonistic**. These observations underscore the notion that environmental changes can act separately on proliferating and differentiating cells within the population. Under the conditions used here, the action of TGF-beta s on human keratinocytes was dominant over RA, and TGF-beta s did not seem to be induced as a consequence of RA treatment. This finding is consistent with the fact that RA accelerated, rather than inhibited, proliferation in raft cultures. Collectively, our data suggest that the effects of both factors on epidermal growth and differentiation are multifaceted and the extent to which their action is coupled in keratinocytes may vary under different conditions and/or in different species.

L6 ANSWER 6 OF 12 MEDLINE on STN
AN 91019968 MEDLINE
DN PubMed ID: 2145653
TI [Acne and its drug treatment].
Die Akne und ihre medikamentose Behandlung.
AU Buchner S A
CS Dermatologische Universitatsklinik Basel.
SO Therapeutische Umschau. Revue therapeutique, (1990 Aug) 47 (8) 670-4.
Journal code: 0407224. ISSN: 0040-5930.
CY Switzerland
DT Journal; Article; (JOURNAL ARTICLE)
LA German
FS Priority Journals
EM 199011
ED Entered STN: 19910117
Last Updated on STN: 19910117
Entered Medline: 19901109
AB The most common disease of the pilosebaceous follicle is acne vulgaris. The primary detectable pathologic defect in acne is abnormal **keratinization** of the follicular epithelium, resulting in a retention hyperkeratosis. The primary lesion produced by this process, the comedo, ist the precursor of most other acne lesions. These include inflammatory papules, pustules and nodules. Treatment principles are directed against known pathogenic factors. The major topical modalities that are currently being used include tretinoin, benzoyl peroxide and topical antibiotics. Benzoyl peroxide is a powerful antibacterial agent. Topical erythromycin and clindamycin appear to have equivalent efficacy. A major treatment advance has been heralded by the use of oral 13-cis **retinoic** acid (isotretinoin) in the management of patients with severe nodulocystic acne, acne conglobata and acne fulminans. Isotretinoin is teratogenic and should not be given to women of childbearing age.

L6 ANSWER 7 OF 12 MEDLINE on STN
AN 88048498 MEDLINE
DN PubMed ID: 2445304
TI **Retinoic** acid alters the **keratinization** of cultured rat sublingual keratinocytes in vitro.
AU Buckley A; Middleton M C
CS Department of Pathology, Vanderbilt University, Medical Center North, Nashville, TN 37232.
SO Archives of dermatological research, (1987) 279 (4) 257-65.
Journal code: 8000462. ISSN: 0340-3696.
CY GERMANY, WEST: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198711
ED Entered STN: 19900305
Last Updated on STN: 19900305
Entered Medline: 19871130
AB A multilayered, continuously proliferating keratinocyte cell culture has been produced from rat sublingual epithelium. The rate of growth of the cultures was stable throughout long-term culture. **Retinoic** acid (3.3 microM) inhibited the **keratinization** of these cultures. Morphological changes included total loss of tonofilaments within 7 days, decrease in desmosomes, an increase in intercellular spaces, absence of thickened plasma membranes, and elongated and more numerous cytoplasmic projections. Exposure to **retinoic** acid (3.3 microM) for 33 days did not affect the growth rates of the cultures, as estimated from the protein and DNA content per flask. **Retinoic** acid (3.3 microM) reduced the polyacrylamide gel electrophoresis protein profile within 3 days of treatment and produced reductions in the incorporation of amino

acids into keratins of molecular weights 62,000 and 60,000 within 24 h. All five keratin polypeptides showed a reduced incorporation rate after treatment for 3 days. This inhibition was reversible. Protein synthesis of nonkeratins was not detectably affected by **retinoid** treatment.

L6 ANSWER 8 OF 12 MEDLINE on STN
AN 85284246 MEDLINE
DN PubMed ID: 2411481
TI Conformational restrictions of the **retinoid** skeleton.
AU Dawson M I; Hobbs P D; Chan R; Derdzinski K; Helmes C T; Chao W; Meierhenry E; Schiff L J
NC CA30512 (NCI)
CA32428 (NCI)
NO1-CP-05600 (NCI)
+
SO Ciba Foundation symposium, (1985) 113 6-28.
Journal code: 0356636. ISSN: 0300-5208.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198510
ED Entered STN: 19900320
Last Updated on STN: 19970203
Entered Medline: 19851015
AB A series of conformationally restricted **retinoids** has been synthesized and assayed for biological activity. These compounds have aromatic rings in place of selected double bonds of the tetraene side-chain of **retinoic** acid and could be considered as analogues of **retinoic** acid in which some of the double bonds possess s-cis topology. Thus far, analogues in which the bonds corresponding to the (5,7E)-, (7,9E)-, (9,11,13E)- and (11,13E)-double bond systems of **retinoic** acid are restricted to a cisoid conformation have been studied. Analogues were screened for their ability to reverse **keratinization** in hamster tracheal organ culture and to inhibit the induction of ornithine decarboxylase in mouse epidermis. Selected compounds were also screened in the antipapilloma assay in mice. The toxicity of some analogues on intraperitoneal injection in mice was determined.

L6 ANSWER 9 OF 12 MEDLINE on STN
AN 85033561 MEDLINE
DN PubMed ID: 6208361
TI Conformationally restricted **retinoids.**
AU Dawson M I; Hobbs P D; Derdzinski K; Chan R L; Gruber J; Chao W R; Smith S; Thies R W; Schiff L J
NC CA30512 (NCI)
CA32428 (NCI)
N01-CP-05600 (NCI)
+
SO Journal of medicinal chemistry, (1984 Nov) 27 (11) 1516-31.
Journal code: 9716531. ISSN: 0022-2623.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198412
ED Entered STN: 19900320
Last Updated on STN: 19970203
Entered Medline: 19841210
AB A series of conformationally restricted **retinoids** was synthesized and screened in two assays used to measure the ability of **retinoids** to control cell differentiation, namely, the reversal of **keratinization** in tracheal organ culture from vitamin A deficient hamsters and the inhibition of the induction of mouse epidermal ornithine decarboxylase by a tumor promoter. These compounds had bonds corresponding to selected bonds of the E-tetraene chain of **retinoic** acid (1) held in a planar cisoid conformation by inclusion in an aromatic ring. The meta-substituted analogue 3 of 4-[(E)-2-methyl-4-(2,6,6-trimethylcyclohexenyl)-1,3-butadienyl+ ++]benzoic acid (2) was far less active than 2 in both assays. In contrast, the vinyl homologue of 2 (4) and the 7,8-dihydro and 7,8-methano analogues (5 and 6) had activity comparable to that of 2. Analogues of 4-[(E)-2-(1,1,4,4-tetramethyl-1,2,3,4-tetrahydro-6-naphthyl)propenyl] benzoic acid (7) were also screened. Replacement of the tetrahydronaphthalene ring of 7 by a benzonorbornenyl group (9) significantly reduced activity, as did removal of the vinylic methyl group

from 9 (10). Replacement of the propenyl group of 9 by a cyclopropane ring (12) also reduced activity. Replacement of the tetrahydronaphthalene ring of 7 by 4,4-dimethyl-3,4-dihydro-2H-1-benzopyran and -benzothiopyran rings (13 and 14) also decreased activity. Inclusion of the 7,9 double bond system of 1 in an aromatic ring (15 and 16) reduced activity, whereas inclusion of the 5,7 double bond system in an aromatic ring enhanced activity (7 and 19). Inclusion of the 11,13 and 9,11,13 double bond systems in aromatic rings (2 and 18) also reduced activity below that of 1. **Retinoic** acid, 7, 13, 14, and 19 inhibited papilloma tumor formation in mice. Toxicity testing indicated that 7 was more toxic than 1, 13, 14, and 19, 19 was more toxic than 1, and 13 and 14 were less toxic than 1.

L6 ANSWER 10 OF 12 MEDLINE on STN
AN 78056558 MEDLINE
DN PubMed ID: 73259
TI [Progress in medicine in individual presentations, XI. Modern forms of therapy in acne].
Fortschritte der Medizin in Einzeldarstellungen, XI.
AU Fanta D; Niebauer G
SO Wiener klinische Wochenschrift, (1977 Oct 28) 89 (20) 677-83. Ref: 75
Journal code: 21620870R. ISSN: 0043-5325.
CY Austria
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LA German
FS Priority Journals
EM 197801
ED Entered STN: 19900314
Last Updated on STN: 19900314
Entered Medline: 19780127
AB Several pathogenetic factors contribute to the development of acne vulgaris. These include genetic predisposition, hormonal influences, increasing sebaceous secretion, bacterial colonization of the follicle and **keratinization** defects in the follicular epithelium. Modern acne therapy can take specific forms on the basis of recent research on pathogenesis. Sebostatic therapy can be performed by the topical application of benzoyl peroxide or the systemic administration of hormones (oestrogens, antiandrogens). Local treatment with **retinoic** has proved optimal in achieving a comedolytic effect. Moreover, the long-term use of antibiotics--tetracyclines, erythromycin systemically or benzoyl peroxide topically--is beneficial in respect to a reduction in Propionibacterium acnes. Experiments with immunological therapy are still in the early stages. Optimum results are obtained by the rational combination of several therapeutic modalities adapted to the type of acne to be treated.

L6 ANSWER 11 OF 12 MEDLINE on STN
AN 78006849 MEDLINE
DN PubMed ID: 908846
TI Effects of **retinoic** acid on embryonic chick skin.
AU Peck G L; Elias P M; Wetzel B
SO Journal of investigative dermatology, (1977 Nov) 69 (5) 463-76.
Journal code: 0426720. ISSN: 0022-202X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 197711
ED Entered STN: 19900314
Last Updated on STN: 19900314
Entered Medline: 19771130
AB The influence of vitamin A on differentiating epithelia was examined in explants of skin from 14-day chick embryos exposed to **retinoic** acid (RA) in low, moderate, and high doses. The changes observed in RA-treated cultures are both dose- and time-dependent and are reversible when explants are transferred to control medium. The periderm sloughs prematurely and horizontal stratification is lost. **Keratinization** is inhibited and fewer desmosomes and tonofilaments are seen. Surface epidermal cells develop microvilli, bulge upwards, and detach. Golgi elements, rough endoplasmic reticulum, and polyribosomes are unusually prominent. Mucin granules form and gland-like structures develop with intercellular canaliculi characterized by tight junctions, brush borders, and dense secretory contents. On the basis of present evidence there are several possible mechanisms by which RA could alter epidermal differentiation. RA-induced gaps in the basal lamina allow direct contact between epidermal basal cells and fibroblasts and collagen fibers which could result in inappropriate dermal signals reaching the epidermis. In

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younger embryos the entire epidermis, including the mitotically inactive surface cells, appears to respond to RA, and this could imply an epigenetic modulation of cell phenotype. Finally, after the formation of a stratum corneum in older embryos only the relatively undifferentiated basal layer shows a metaplastic response, indicating that RA could be acting directly on the genome.

L6 ANSWER 12 OF 12 MEDLINE on STN
AN 77168279 MEDLINE
DN PubMed ID: 404431
TI Effects of depot injections of retinyl palmitate on 7,12-dimethylbenz[a]anthracene-induced preneoplastic changes in rat skin.
AU Brown I V; Lane B P; Pearson J
SO Journal of the National Cancer Institute, (1977 May) 58 (5) 1347-55.
Journal code: 7503089. ISSN: 0027-8874.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 197706
ED Entered STN: 19900313
Last Updated on STN: 19900313
Entered Medline: 19770622
AB The preneoplastic skin changes usually induced by topical application of 7,12-dimethylbenz[a]anthracene (DMBA) to adult rat skin did not appear when animals were treated locally with depot im injections of high doses of retinyl palmitate (RP) prior to exposure to the carcinogen. The epidermal histology after RP-DMBA treatment was similar to that seen in areas exposed to RP alone. **Keratinization** was inhibited but there was no cellular atypia, evidence of cell injury, or mucous metaplasia. Other features were hyperplasia with acanthosis and thickened stratum granulosum, parakeratosis, intercellular edema, and loss of hair overlying the injection site. Ultrastructurally, the epidermal cells contained conspicuously fewer tonofibrils and increased dense chromatin, when compared to control cells. Skin changes observed following treatment of littermates with DMBA alone included the appearance of giant tumor cells, dyskeratotic cells, nuclear hyperchromatism, increased nucleocytoplasmic ratio, and pleomorphic nuclei and nucleoli. oss of desmosomes, increased tonofibrils, and defects in the basement membrane with epithelial projections into the dermis were also seen. These preneoplastic changes did not regress when application with DMBA was discontinued after 6 weeks; exposure to the carcinogen for longer than 6 weeks resulted in an exacerbation of the abnormal state. RP had profound effects on rat epidermis that interfered with the effects of a potent skin carcinogen. The mechanisms underlying the phenomenon have not been defined. The use of depot injections of the vitamin which avoids both systemic toxicity and the local irritation seen with topical exposure could serve as a model in which the anticarcinogenesis properties of **retinoids** could be explored.

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=> d his

     (FILE 'HOME' ENTERED AT 14:20:25 ON 20 JUL 2004)

     FILE 'MEDLINE' ENTERED AT 14:20:59 ON 20 JUL 2004
L1         68418 S RETINO?
L2          2524 S RAR
L3           357 S L2 AND ANTAGONIST?
L4            13 S L3 AND KERATIN?
L5          3655 S L1 AND ANTAGONIST?
L6            12 S L5 AND KERATINIZATION

=> l2 and psoriasis
L2 IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> s l2 and psoriasis
          20851 PSORIASIS
L7           19 L2 AND PSORIASIS

=> s l7 and antagonist?
         469098 ANTAGONIST?
L8            5 L7 AND ANTAGONIST?

=> d 1-5 bib abs kwic
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L8 ANSWER 1 OF 5 MEDLINE on STN
AN 2000435655 MEDLINE
DN PubMed ID: 10329471
TI Identification of the AP1-antagonism domain of retinoic acid receptors.
AU DiSepio D; Sutter M; Johnson A T; Chandraratna R A; Nagpal S
CS Department of Biology, Allergan Inc., Irvine, California 92713, USA.
SO Molecular cell biology research communications : MCBRC, (1999 Apr) 1 (1) 7-13.
Journal code: 100889076. ISSN: 1522-4724.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200009
ED Entered STN: 20000928
Last Updated on STN: 20000928
Entered Medline: 20000921
AB Retinoids are therapeutically effective in the treatment of **psoriasis**, photoaging, acne, and certain cancers. Some of the therapeutic actions of retinoids can be ascribed to retinoic acid receptor (**RAR**)-mediated antagonism of AP1-dependent gene expression. The increased activity of transcription factor AP1, a complex of oncoproteins Jun and Fos, is associated with cell growth and proliferation. Retinoids, on the other hand, inhibit cell proliferation and affect differentiation, activities that possibly stem from an antagonism of AP1-mediated gene expression by RARs. To gain insight into the molecular mechanism of **RAR**-AP1 interaction, we have identified the regions of the **RAR** required for AP1 antagonism. We demonstrate that the AP1 antagonism domain of **RAR** is a complex of the core of the DNA binding domain and the hydrophobic zipper region. Further, both monomeric **RAR** and **RAR**-RXR heterodimers inhibit the expression of an AP1 reporter. CREB binding protein (CBP) has been described as a cofactor for AP1, various nuclear hormone receptor proteins including RARs, and certain other transcription factors and is required for their transactivation properties. Therefore, CBP has been proposed as a common limiting cofactor that can account for inhibition of AP1-dependent gene expression by RARs. Interestingly, however, our results along with previously reported observations suggest that in addition to CBP, there may be other limiting cofactor(s) responsible for mutual transrepression of **RAR** and AP1.
AB Retinoids are therapeutically effective in the treatment of **psoriasis**, photoaging, acne, and certain cancers. Some of the therapeutic actions of retinoids can be ascribed to retinoic acid receptor (**RAR**)-mediated antagonism of AP1-dependent gene expression. The increased activity of transcription factor AP1, a complex of oncoproteins Jun and Fos, is. . . that possibly stem from an antagonism of AP1-mediated gene expression by RARs. To gain insight into the molecular mechanism of **RAR**-AP1 interaction, we have identified the regions of the **RAR** required for AP1 antagonism. We demonstrate that the AP1 antagonism domain of **RAR** is a complex of the core of the DNA binding domain and the hydrophobic zipper region. Further, both monomeric **RAR** and **RAR**-RXR heterodimers inhibit the expression of an AP1 reporter. CREB binding protein (CBP) has been described as a cofactor for AP1,. . . previously reported observations suggest that in addition to CBP, there may be other limiting cofactor(s) responsible for mutual transrepression of **RAR** and AP1.
CT . . .
*Receptors, Retinoic Acid: ME, metabolism
Recombinant Proteins: CH, chemistry
Recombinant Proteins: GE, genetics
Recombinant Proteins: ME, metabolism
Trans-Activators: ME, metabolism
***Transcription Factor AP-1: AI, antagonists & inhibitors**
Transcription Factors: CH, chemistry
Transcription Factors: GE, genetics
Transcription Factors: ME, metabolism
Transfection

L8 ANSWER 2 OF 5 MEDLINE on STN
AN 2000291536 MEDLINE
DN PubMed ID: 10828316
TI Recent developments in receptor-selective retinoids.
AU Nagpal S; Chandraratna R A
CS Retinoid Research, Department of Biology and Chemistry, Allergan Inc., Irvine, CA-92713, USA.
SO Current pharmaceutical design, (2000 Jun) 6 (9) 919-31. Ref: 71
Journal code: 9602487. ISSN: 1381-6128.

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CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200007
ED Entered STN: 20000811
Last Updated on STN: 20000811
Entered Medline: 20000731
AB Natural (all trans-retinoic acid, RA) and synthetic retinoids exhibit potent anti-proliferative, normalization of differentiation and anti-inflammatory activities which appear to account for their therapeutic effects in acne, **psoriasis**, photoaging, precancerous lesions and established cancers. Although RA has shown considerable promise in dermatologic indications, certain side effects have restricted its use as a choice of agent for chronic administration. Systematic synthesis of receptor-selective retinoids has resulted in two topical drugs, Tazorac/Zorac (tazarotene) and Differin (adapalene). Tazorac is indicated for **psoriasis** and acne and Differin gel for the treatment of acne. These drugs bind to the retinoic acid receptor (**RAR**) family members. Various **RAR** subtype-specific and function-selective retinoids have been synthesized. These retinoids, which are in various stages of pre-clinical development for the treatment of cancers, **psoriasis** and as an antidote to Accutane-mediated mucocutaneous toxicity, will also be discussed in this review. Discovery of another retinoid receptor, retinoid X receptor (RXR), revealed that RXR-specific retinoids already existed in retinoid chemical libraries. Structure activity relationship studies based upon binding and transactivation assays led to the synthesis of RXR-specific ligands with high affinities for RXR subtypes. These compounds were found to be effective in the treatment of hyperglycemia in animal models of type II diabetes. The discovery of novel retinoids along with an increased understanding of the biological functions and mechanisms of action of retinoid receptors are likely to result in improved treatments for existing responsive indications and identification of new retinoid therapeutic targets.
AB . . . retinoids exhibit potent anti-proliferative, normalization of differentiation and anti-inflammatory activities which appear to account for their therapeutic effects in acne, **psoriasis**, photoaging, precancerous lesions and established cancers. Although RA has shown considerable promise in dermatologic indications, certain side effects have restricted. . . Systematic synthesis of receptor-selective retinoids has resulted in two topical drugs, Tazorac/Zorac (tazarotene) and Differin (adapalene). Tazorac is indicated for **psoriasis** and acne and Differin gel for the treatment of acne. These drugs bind to the retinoic acid receptor (**RAR**) family members. Various **RAR** subtype-specific and function-selective retinoids have been synthesized. These retinoids, which are in various stages of pre-clinical development for the treatment of cancers, **psoriasis** and as an antidote to Accutane-mediated mucocutaneous toxicity, will also be discussed in this review. Discovery of another retinoid receptor,. . .
CT . . .
pharmacology
Drug Design
Gene Expression: DE, drug effects
Naphthalenes: PD, pharmacology
Nicotinic Acids: PD, pharmacology
Receptors, Retinoic Acid: AG, agonists
***Receptors, Retinoic Acid: AI, antagonists & inhibitors**
Receptors, Retinoic Acid: GE, genetics
Receptors, Retinoic Acid: ME, metabolism
*Retinoids: CH, chemistry
Retinoids: PD, pharmacology
Transcription Factors: AG, agonists
***Transcription Factors: AI, antagonists & inhibitors**
Transcription Factors: GE, genetics
Transcription Factors: ME, metabolism

L8 ANSWER 3 OF 5 MEDLINE on STN
AN 2000105744 MEDLINE
DN PubMed ID: 10637371
TI Therapeutic applications for ligands of retinoid receptors.
AU Thacher S M; Vasudevan J; Chandraratna R A
CS Retinoid Research, Departments of Biology and Chemistry, Allergan Inc., Irvine, California 92623, USA.
SO Current pharmaceutical design, (2000 Jan) 6 (1) 25-58. Ref: 216
Journal code: 9602487. ISSN: 1381-6128.

10676089

CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200003
ED Entered STN: 20000327
Last Updated on STN: 20000327
Entered Medline: 20000315
AB Synthetic retinoids, ligands for the **RAR** and RXR members of the steroid/thyroid superfamily of nuclear hormone receptors, are used for the treatment of **psoriasis**, acne, photoaging and cancer. Retinoid mechanisms of action for these conditions largely involve effects on epithelial differentiation and modulation of inflammation with some impact on the immune system. Retinoid medicinal chemistry in recent years has identified ligands highly specific for one of the three **RAR** subtypes (**RAR**-alpha) and for the RXR family of receptors, as well as **antagonists** for the RARs, RARalpha and the RXRs. Structure-activity relationships among the novel retinoid classes are reviewed along with potential therapeutic activities and side effects. **RAR**-alpha specific retinoids inhibit cancer cell growth but lack other retinoid toxicities, including skin irritation now ascribed to **RAR**-gama. RXR-specific retinoids lower blood glucose in animal models of type 2 diabetes albeit with a potential for mild hypothyroidism. Function-selective retinoids, especially a class of **RAR antagonists** called inverse agonists, have unexpected gene regulatory activity. Given the diverse properties and tissue distributions of the retinoid receptors, synthesis of additional classes of receptor-specific and function-selective ligands has the potential to produce novel therapeutic applications.
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CT Check Tags: Human
Animals
Drug Design
Ligands
*Receptors, Retinoic Acid: AG, agonists
***Receptors, Retinoic Acid: AI, antagonists & inhibitors**
Receptors, Retinoic Acid: CH, chemistry
Receptors, Retinoic Acid: ME, metabolism
Retinoids: CH, chemistry
Retinoids:. . .

L8 ANSWER 4 OF 5 MEDLINE on STN
AN 1999004261 MEDLINE
DN PubMed ID: 9787993
TI Current research and future developments in retinoids: oral and topical agents.
AU Chandraratna R A
CS Allergan, Irvine, California 92612, USA.
SO Cutis; cutaneous medicine for the practitioner, (1998 Feb) 61 (2 Suppl) 40-5. Ref: 19
Journal code: 0006440. ISSN: 0011-4162.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199901

10676089

ED Entered STN: 19990115
Last Updated on STN: 19990115
Entered Medline: 19990107

AB The retinoids are a class of small molecules capable of affecting biological systems in a fundamental way by interacting with a variety of nuclear receptors and affecting gene transcription. As such, they have powerful therapeutic potential in the treatment of a variety of diseases. However, non-selective retinoid drugs that indiscriminately activate many or all of the different retinoid receptors and their signaling pathways will invariably produce both undesirable and beneficial effects. Therefore, current and future retinoid research must employ a rational approach to drug discovery, the goal of which is to design retinoid drugs with sufficient receptor or function selectivity that only those biological systems relevant to a specific disease are affected. Tazarotene is a retinoid with properties that are a result of this rational approach to drug discovery. Its molecular structure was engineered in such a way as to make it selective for the retinoic acid receptor (**RAR**) class of nuclear receptors over retinoid X receptors (RXRs), with preferential activation of **RAR** beta and **RAR** gamma over **RAR** alpha. It was further engineered to possess clinically favorable pharmacokinetic properties. To date, all retinoid drugs available for therapeutic use are retinoid agonists; they bind to retinoid receptors and facilitate gene transcription. However, ongoing research has developed retinoid **antagonists** (that bind to receptors without activating gene transcription) and inverse agonists (that bind to receptors and inhibit gene transcription). These new drugs and other retinoids currently under development represent new opportunities for the treatment of a variety of disorders in dermatology, oncology, and metabolic disease.

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CT . . . Human
Administration, Oral
Administration, Topical
Animals
California
Forecasting
Guinea Pigs
*Nicotinic Acids: AD, administration & dosage
*Nicotinic Acids: CH, chemistry
Psoriasis: DT, drug therapy
Research: TD, trends
*Retinoids: AD, administration & dosage
*Retinoids: CH, chemistry

L8 ANSWER 5 OF 5 MEDLINE on STN
AN 95122546 MEDLINE
DN PubMed ID: 7822331
TI Separation of transactivation and AP1 antagonism functions of retinoic acid receptor alpha.
AU Nagpal S; Athanikar J; Chandraratna R A
CS Department of Biology, Allergan Inc., Irvine, California 92713.
SO Journal of biological chemistry, (1995 Jan 13) 270 (2) 923-7.
Journal code: 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199502
ED Entered STN: 19950223
Last Updated on STN: 19970203
Entered Medline: 19950213

AB Retinoic acid receptors (RARs) regulate gene expression either by directly binding to the **RAR**-responsive elements or by antagonizing the action of c-Jun/c-Fos (AP1). AP1 is involved in the expression of metalloproteases, cytokines and other factors which play critical roles in the turnover of extracellular matrix, inflammation and hyperproliferation in diseases such as **psoriasis**, rheumatoid arthritis and in tumor metastases. We demonstrate here that synthetic retinoids inhibit

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12-O-tetradecanoylphorbol-14-acetate-induced transcription from the stromelysin AP1 motif through **RAR** alpha, -beta, and -gamma. Interestingly, these diaryl acetylenic retinoids, which are potent agonists only for **RAR** beta and **RAR** gamma, but not for **RAR** alpha, in transactivation assays, are able to inhibit AP1-dependent gene expression through **RAR** alpha. Thus these analogs can differentially affect the transactivation and AP1 **antagonistic** functions of **RAR** alpha. These results demonstrate that the transactivation and AP1 **antagonistic** functions are separable, and it should be possible to develop retinoids that are completely specific for AP1 antagonism through all RARs. Furthermore, using an **RAR**-selective ligand, we also demonstrate the separation of ligand binding and AP1 antagonism functions of RARs.

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CT . . . Check Tags: Human
Base Sequence
DNA Primers
Hela Cells
Ligands
Molecular Sequence Data
*Receptors, Retinoic Acid: PH, physiology
*Trans-Activation (Genetics)
***Transcription Factor AP-1: AI, antagonists & inhibitors**

=>

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L10 ANSWER 1 OF 1 MEDLINE on STN
AN 1999004258 MEDLINE
DN PubMed ID: 9787990
TI Excerpt of panel discussion from symposium.
AU Anonymous
SO Cutis; cutaneous medicine for the practitioner, (1998 Feb) 61 (2 Suppl) 30-5.
Journal code: 0006440. ISSN: 0011-4162.
CY United States
DT Conference; Conference Article; (CONGRESSES)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199901
ED Entered STN: 19990115
Last Updated on STN: 19990115
Entered Medline: 19990107
AB In summary, then, tazarotene is a selective **RAR agonist** . It has clinical efficacy similar to fluocinonide cream, but no risk of atrophogenicity, no tachyphylaxis, and longer duration of remission than we see with topical corticosteroids. Adverse effects are erythema, burning, and pruritus. Such effects are reduced and efficacy improved by combining the treatment with topical corticosteroids. It is also useful with ultraviolet B phototherapy. PUVA should be the next treatment modality to be explored in combination with tazarotene. It is useful on the scalp and in paronychial areas and, in fact, other areas that are refractory to other treatments your patients may be using. It is not photosensitizing so far, but more work needs to be done to prove that. It is pregnancy category X. If it is administered systemically, it is teratogenic. When administered topically, it is not. It is not lipophilic, so it is not stored in fat and is rapidly eliminated.
AB In summary, then, tazarotene is a selective **RAR agonist** . It has clinical efficacy similar to fluocinonide cream, but no risk of atrophogenicity, no tachyphylaxis, and longer duration of remission. . .
CT . . .
effects
*Nicotinic Acids: AD, administration & dosage
Nicotinic Acids: AE, adverse effects
Pregnancy
Pregnancy Complications, Infectious: DT, drug therapy
Prognosis
***Psoriasis: DT, drug therapy**
Treatment Outcome

10676089

=> d 1-6 bib abs kwic

L14 ANSWER 1 OF 6 MEDLINE on STN
AN 2004280965 IN-PROCESS
DN PubMed ID: 15180475
TI Peroxisome proliferator-activated receptors as new molecular targets in psoriasis.
AU Kuenzli Stephane; Saurat Jean-Hilaire
CS Department of Dermatology, University Hospital, Geneva, Switzerland.. stephane.kuenzli@medecine.unige.ch
SO Current drug targets. Inflammation and allergy, (2004 Jun) 3 (2) 205-11. Journal code: 101160019. ISSN: 1568-010X.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS IN-PROCESS; NONINDEXED; Priority Journals
ED Entered STN: 20040608
Last Updated on STN: 20040625
AB While **psoriasis** is upon the age of biological treatments, additional researches have led to other new therapies for **psoriasis**, including targets aimed at nuclear receptors. PPARs are members of the nuclear-hormone-receptor superfamily, including **retinoid** receptors and vitamin D receptors. Recent works have highlighted the role of PPARs, which transduce a wide variety of signals into a set of cellular responses at the level of gene transcription, as critical regulators of cutaneous homeostasis in regulating differentiation, proliferation, and inflammatory responses of the skin. PPAR **agonists** or **antagonists** may therefore, hold promise as interesting compounds for the treatment of various epidermal disorders characterized by inflammation, hyperproliferation and aberrant differentiation, such as **psoriasis**.
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L14 ANSWER 2 OF 6 MEDLINE on STN
AN 2001539396 MEDLINE
DN PubMed ID: 11586072
TI Retinoids--which dermatological indications will benefit in the near future?.
AU Zouboulis C C
CS Department of Dermatology, University Medical Center Benjamin Franklin, The Free University of Berlin, Berlin, Germany.. zouboulis@medizin.fu-berlin.de
SO Skin pharmacology and applied skin physiology, (2001 Sep-Oct) 14 (5) 303-15. Ref: 90
Journal code: 9807277. ISSN: 1422-2868.
CY Switzerland
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200112
ED Entered STN: 20011008
Last Updated on STN: 20020122
Entered Medline: 20011204
AB **Retinoids** are compounds with pleiotropic functions and a relatively selective targeting of certain skin structures. They are vitamins, because **retinol** (vitamin A) is not synthesized in the body and must be derived from diet, but also hormones with intracrine activity, because **retinol** is transformed into molecules that bind to nuclear receptors, exhibit their activity, and are subsequently inactivated. **Retinoids** exert their effects on target cells by binding and activating nuclear **retinoid** receptors. **Retinoid** receptors bind their ligands in form of dimers. Heterodimers can be formed between two different **retinoid** receptor molecules but also between **retinoid** X receptors and the

vitamin D receptor as well as the triiodothyronin receptor. This fact indicates complex interactions between **retinoids** and further hormonal signal transduction molecules. Interaction of **retinoid** receptors with transcriptional factors activated by other signal transduction mechanisms, e.g. AP-1, may provide dissociation of the **retinoid** effects. **Retinoids** can exhibit **agonistic** activity but also be neutral **antagonists** and inverse **agonists**. Topical and oral **retinol**, tretinoin, isotretinoin, and bexarotene, topical alitretinoin, retinaldehyde, motretinide, adapalene, tazarotene, and systemin acitretin compose the list of launched **retinoids**. **Psoriasis** and related disorders, congenital disorders of keratinization, acne, photoaging and hypovitaminosis A are classical approved indications of **retinoid** treatment, whereas cutaneous T-cell lymphoma, AIDS-associated Kaposi's sarcoma, acute promyelocytic leukemia and actinic lentigines were currently confirmed. In addition, **retinoids** have been successfully used in several other dermatoses, e.g. epithelial precanceroses and tumors, seborrhea, rosacea and acneiform dermatoses, lichen planus, eosinophilic folliculitis, condylomata accuminata, lichen sclerosus and atrophicus. Highly receptor selective molecules, **retinoic** acid receptor-beta-inducers, AP-1 complex **antagonists**, and inverse **agonists** will be probably lead the **retinoid** development in the near future. New, more effective and less toxic **retinoids**, alone or in combination with other drugs and new delivery systems may provide therapeutic solutions for benign and malignant proliferative skin diseases, such as **psoriasis** and non-melanoma tumors, cancer chemoprevention and differentiation therapy.

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CT Check Tags: Human
Animals
Retinoids: AG, agonists
*Retinoids: TU, therapeutic use
Skin Diseases: DI, diagnosis
*Skin Diseases: DT, drug therapy

L14 ANSWER 3 OF 6 MEDLINE on STN
AN 2000291536 MEDLINE

10676089

DN PubMed ID: 10828316
TI Recent developments in receptor-selective retinoids.
AU Nagpal S; Chandraratna R A
CS Retinoid Research, Department of Biology and Chemistry, Allergan Inc., Irvine, CA-92713, USA.
SO Current pharmaceutical design, (2000 Jun) 6 (9) 919-31. Ref: 71
Journal code: 9602487. ISSN: 1381-6128.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200007
ED Entered STN: 20000811
Last Updated on STN: 20000811
Entered Medline: 20000731
AB Natural (all trans-**retinoic** acid, RA) and synthetic **retinoids** exhibit potent anti-proliferative, normalization of differentiation and anti-inflammatory activities which appear to account for their therapeutic effects in acne, **psoriasis**, photoaging, precancerous lesions and established cancers. Although RA has shown considerable promise in dermatologic indications, certain side effects have restricted its use as a choice of agent for chronic administration. Systematic synthesis of receptor-selective **retinoids** has resulted in two topical drugs, Tazorac/Zorac (tazarotene) and Differin (adapalene). Tazorac is indicated for **psoriasis** and acne and Differin gel for the treatment of acne. These drugs bind to the **retinoic** acid receptor (RAR) family members. Various RAR subtype-specific and function-selective **retinoids** have been synthesized. These **retinoids**, which are in various stages of pre-clinical development for the treatment of cancers, **psoriasis** and as an antidote to Accutane-mediated mucocutaneous toxicity, will also be discussed in this review. Discovery of another **retinoid** receptor, **retinoid** X receptor (RXR), revealed that RXR-specific **retinoids** already existed in **retinoid** chemical libraries. Structure activity relationship studies based upon binding and transactivation assays led to the synthesis of RXR-specific ligands with high affinities for RXR subtypes. These compounds were found to be effective in the treatment of hyperglycemia in animal models of type II diabetes. The discovery of novel **retinoids** along with an increased understanding of the biological functions and mechanisms of action of **retinoid** receptors are likely to result in improved treatments for existing responsive indications and identification of new **retinoid** therapeutic targets.
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CT . . . Tags: Human
Dermatologic Agents: PD, pharmacology
Drug Design
Gene Expression: DE, drug effects
Naphthalenes: PD, pharmacology
Nicotinic Acids: PD, pharmacology

Receptors, Retinoic Acid: AG, agonists
***Receptors, Retinoic Acid: AI, antagonists & inhibitors**
Receptors, Retinoic Acid: GE, genetics
Receptors, Retinoic Acid: ME, metabolism
*Retinoids: CH, chemistry
Retinoids: PD, pharmacology
Transcription Factors: AG, agonists
***Transcription Factors: AI, antagonists & inhibitors**
Transcription Factors: GE, genetics
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L14 ANSWER 4 OF 6 MEDLINE on STN
AN 2000105744 MEDLINE
DN PubMed ID: 10637371
TI Therapeutic applications for ligands of retinoid receptors.
AU Thacher S M; Vasudevan J; Chandraratna R A
CS Retinoid Research, Departments of Biology and Chemistry, Allergan Inc., Irvine, California 92623, USA.
SO Current pharmaceutical design, (2000 Jan) 6 (1) 25-58. Ref: 216
Journal code: 9602487. ISSN: 1381-6128.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
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FS Priority Journals
EM 200003
ED Entered STN: 20000327
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Entered Medline: 20000315
AB Synthetic **retinoids**, ligands for the RAR and RXR members of the steroid/thyroid superfamily of nuclear hormone receptors, are used for the treatment of **psoriasis**, acne, photoaging and cancer. **Retinoid** mechanisms of action for these conditions largely involve effects on epithelial differentiation and modulation of inflammation with some impact on the immune system. **Retinoid** medicinal chemistry in recent years has identified ligands highly specific for one of the three RAR subtypes (RAR-alpha) and for the RXR family of receptors, as well as **antagonists** for the RARs, RARalpha and the RXRs. Structure-activity relationships among the novel **retinoid** classes are reviewed along with potential therapeutic activities and side effects. RAR-alpha specific **retinoids** inhibit cancer cell growth but lack other **retinoid** toxicities, including skin irritation now ascribed to RAR-gama. RXR-specific **retinoids** lower blood glucose in animal models of type 2 diabetes albeit with a potential for mild hypothyroidism. Function-selective **retinoids** , especially a class of RAR **antagonists** called inverse **agonists**, have unexpected gene regulatory activity. Given the diverse properties and tissue distributions of the **retinoid** receptors, synthesis of additional classes of receptor-specific and function-selective ligands has the potential to produce novel therapeutic applications.
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CT Check Tags: Human
Animals
Drug Design
Ligands

10676089

*Receptors, Retinoic Acid: AG, agonists
*Receptors, Retinoic Acid: AI, antagonists & inhibitors
Receptors, Retinoic Acid: CH, chemistry
Receptors, Retinoic Acid: ME, metabolism
Retinoids: CH, chemistry
Retinoids:. . .

L14 ANSWER 5 OF 6 MEDLINE on STN
AN 95122546 MEDLINE
DN PubMed ID: 7822331
TI Separation of transactivation and AP1 antagonism functions of retinoic acid receptor alpha.
AU Nagpal S; Athanikar J; Chandraratna R A
CS Department of Biology, Allergan Inc., Irvine, California 92713.
SO Journal of biological chemistry, (1995 Jan 13) 270 (2) 923-7.
Journal code: 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
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ED Entered STN: 19950223
Last Updated on STN: 19970203
Entered Medline: 19950213
AB **Retinoic** acid receptors (RARs) regulate gene expression either by directly binding to the RAR-responsive elements or by antagonizing the action of c-Jun/c-Fos (AP1). AP1 is involved in the expression of metalloproteases, cytokines and other factors which play critical roles in the turnover of extracellular matrix, inflammation and hyperproliferation in diseases such as **psoriasis**, rheumatoid arthritis and in tumor metastases. We demonstrate here that synthetic **retinoids** inhibit 12-O-tetradecanoylphorbol-14-acetate-induced transcription from the stromelysin AP1 motif through RAR alpha, -beta, and -gamma. Interestingly, these diaryl acetylenic **retinoids**, which are potent **agonists** only for RAR beta and RAR gamma, but not for RAR alpha, in transactivation assays, are able to inhibit AP1-dependent gene expression through RAR alpha. Thus these analogs can differentially affect the transactivation and AP1 **antagonistic** functions of RAR alpha. These results demonstrate that the transactivation and AP1 **antagonistic** functions are separable, and it should be possible to develop **retinoids** that are completely specific for AP1 antagonism through all RARs. Furthermore, using an RAR-selective ligand, we also demonstrate the separation of ligand binding and AP1 antagonism functions of RARs.
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CT . . . Check Tags: Human
Base Sequence
DNA Primers
Hela Cells
Ligands
Molecular Sequence Data
*Receptors, Retinoic Acid: PH, physiology
*Trans-Activation (Genetics)
***Transcription Factor AP-1: AI, antagonists & inhibitors**

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TI [Retinoids in dermatology].
Retinoides en dermatologie.
AU Saurat J H

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CS Clinique et Policlinique de Dermatologie, hopital cantonal universitaire, Geneve.
SO La Revue du praticien, (1992 Jan 1) 42 (1) 69-75. Ref: 18
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General Review; (REVIEW)
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LA French
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AB **Retinoids** are natural substances, similar to vitamin A, and acting through nuclear receptor on the gene transcription, with a similar mechanism to steroid hormones. Synthetic **retinoids** are used in the treatment of different skin diseases including severe acne, abnormal keratinization, **psoriasis**, epidermoid carcinoma, and inflammatory skin lesions. Systemic or local administration of these compounds acts on the proliferation and differentiation of the skin structure by not clearly understood pathway. This pathway could be either an **agonist**, **antagonist** or substitutive modulation of the natural **retinoid** action or a separate pathway. The different drugs have in common, teratogenic properties, which limit their usefulness.
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